Br. J. clin. Pharmac. (1988), **26**, 1–5

Spontaneous reporting of adverse drug reactions I: The data

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Introduction

Careful clinical observation, by individual physicians, has a long-established role in the evolution of medical knowledge. The publication of individual case reports of suspected adverse drug reactions has been of special value in alerting the medical profession to possible iatrogenic disorders (Venning, 1983). This *non-systematised* (Inman & Vessey, 1978) form of spontaneous reporting of adverse drug reactions has, however, clear limitations: reports are unsolicited, their publication depends on editorial idiosyncracy, only a very small proportion of the reactions that occur can be documented, and a significant proportion of reports may omit critical information (Venulet, 1985). In the aftermath of the thalidomide tragedy most developed countries instituted schemes for the *systematised* collection of adverse drug reaction reports. Although their details differ, they share the essential feature that reports of suspected adverse reactions encountered during clinical practice are solicited from doctors and pharmaceutical companies (and in some instances from dentists, pharmacists and patients) for collection and analysis by a central monitoring agency.

The UK 'yellow card' spontaneous reporting system was established in 1964. It is organised by the Committee on the Safety of Medicines (CSM) which has a statutory responsibility for the collection and dissemination of information relating to adverse drug reactions. In discharging its responsibility the CSM acts independently of the UK regulatory authority (the Licensing Authority), even though the Committee's Secretariat is comprised of civil servants from the Department of Health & Social Security. At the time of the inception of the yellow-card scheme, the chairman of the CSM (the late Sir Derrick Dunlop) gave two guarantees that are still regarded by the Committee as inviolate: first, that all reports would be treated with complete professional confidence by the Committee and its staff; and second, that the Health Ministers would never use the information for disciplinary purposes or for enquiries about prescribing costs. The Committee is prepared to release information about the details of individual reports to *bona fide* enquirers, but it does not reveal the identity of individual patients. Nor does it disclose the name of a reporting doctor to a third party, except in the most unusual circumstances, and only then with the full agreement of the reporter. The Committee believes that changes in this policy would threaten the viability of the yellow card scheme, and has therefore resisted applications for the disclosure of the names of patients and reporting doctors to the Courts, even to the extent of obtaining a Ministerial Certificate of Public Interest.

Characteristics of data-base

The CSM's Adverse Reaction Register contains over 180,000 reports of suspected adverse drug reactions. Because of the difficulties of distinguishing, in individual patients, iatrogenic causes from other aetiologies it is inevitable that reports are based on the clinical judgement of reporting doctors. Yet an investigation of the validity of a random sample of reports (Inman & Price Evans, 1972) indicated that there was reasonable concordance (82%) between initial assessment and re-assessment after follow-up.

The annual number of reports received by the Committee (Figure 1) has increased from 1,415 per annum in 1964 to 15,500 per annum in 1986. Figure 1 shows that there have been two significant and sustained periods of increased reporting. During the mid-1970s reporting rates almost doubled: though the reason is uncertain, this rise coincided with the withdrawal of practolol, the institution of the CSM publication Current Problems, and an insertion of a yellow 'reminder' into general practitioners' prescription (FP10) pads (Inman, 1986). A second increase in the reporting rate occurred in 1986 and was probably

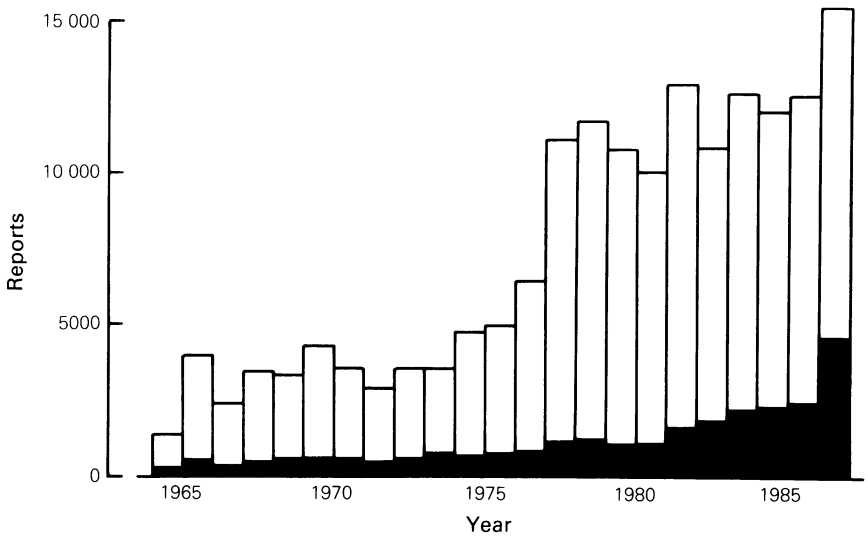

Figure 1 Annual number of reports of suspected adverse drug reactions to the Committee on the Safety of Medicines (□). The solid bars (■) indicate the number of serious reactions.

due to the placement of reporting forms ('yellow slips') into the British National Formulary and general practitioners' prescription pads. The increase in the total number of adverse reaction reports has also (see Figure 1) been mirrored by an increase in the number of reports of severe reactions, though the rise during 1986 has been artificially boosted by a revision of the case-definition of a 'severe' reaction.

Between 80% and 90% of reports of suspected adverse drug reactions are submitted directly to the CSM by doctors. 80% of the medicines used in the National Health Service are prescribed by general practitioners who supply a similar proportion of the adverse drug reactions reported by the medical profession (Griffin, 1987). Analyses of reports by age shows increased reporting rates at the extremes of life (Griffin, 1987; Mann, 1987) with the increase in the elderly mirroring, to some extent, the higher consumption rate of medicines in this group.

Despite the size of the adverse reaction register, there is clear evidence that only a small proportion (rarely exceeding 10 to 15%) of even severe reactions are reported to the Committee. A survey by Speirs *et al.* (1984) found that the 53,685 yellow-cards received between 1972 and 1980 were reported by only 16% of the 122,000 doctors eligible to do so. Studies of reporting rates for individual drugs have shown similar trends. Only 8 out of 53 doctors (15%) whose patients died from thromboembolism whilst taking combined oral contraceptives, reported their cases (Inman & Vessey, 1968); and of deaths from aplastic anaemia, for which phenylbutazone or oxyphenbutazone were probably responsible in 1974–75, only 11% were reported on yellow cards (Inman, 1977). More recently Langman (1986) has estimated that there are 2000 to 2500 episodes of hospital admission per year due to bleeding peptic ulcers attributable to non-steroidal anti-inflammatory drug therapy in patients aged 65 years or more; yet the total number of reports of gastrointestinal haemorrhage (all causes and all ages) attributed to NSAIDs during 1985, and reported to the CSM, was 364 (Committee on the Safety of Medicine, 1986a). In a survey of adverse reactions encountered by general practitioners (Lumley *et al.*, 1986) only 6% were reported on yellow-cards though there was a trend for severe (20%) and moderate (10.6%) reactions to be reported more often than trivial ones (3.6%). Whilst the underreporting of adverse drug reactions is obviously a cause for concern, it is only marginally less than the notification rates of infectious diseases (16% to 22%) for which doctors have a statutory reporting responsibility (Haward, 1973; Jenkinson, 1983).

The reporting of adverse drug reactions which have a long latency, or which occur on withdrawal of therapy, is probably much less than that for acute reactions. Thus, although up to one third of patients receiving chronic neuroleptic treatment develop tardive dyskinesia (Goetz *et al.*, 1982), the Adverse Reaction Register contains only 26 reports of this reaction in patients receiving dopamine antagonists; and despite professional and public disquiet about the frequency and severity of withdrawal reac-

tions in patients on long-term benzodiazepine anxiolytics (Ashton, 1984), there are only 51 reports in the Register.

Because of under-reporting, the number of reported reactions to a particular drug or product needs to be interpreted with caution. There are five independent determinants of the number of yellow cards received by the CSM for a particular drug or product:

1) The number of reports will, to some extent, reflect a drug's inherent acute toxicity and a product with a high therapeutic ratio is thus unlikely to be associated with many reports of suspected adverse reactions. For example, none of the topical dermatological preparations introduced since 1984 have been associated with significant numbers of adverse reactions reports (Committee on the Safety of Medicines, 1986a). Similarly the inhalational anaesthetic agent, isoflurane, which was introduced in the hope that it would lack the hepatotoxic properties of halothane, was not incrimated as a cause of liver damage in 1986 despite the fact that there were 16 reports of hepatotoxicity with halothane during the year. Obviously, the absence of reports of reactions to a particular drug does not invariably confirm its safety, but when assessed in relation to the compound's clinical pharmacological properties it can provide a powerful degree of reassurance. By contrast, drugs with a low therapeutic ratio usually (though not invariably) generate significant numbers of reports of severe reactions. There is however, a tendency for unusual and unexpected reactions to be reported at the expense of well-recognised hazards. For example, the potential nephrotoxicity and hepatotoxicity of cyclosporin A is widely recognised and well-documented, but these reactions have only been the subject of 14 and 1 reports (respectively); there have, however, been 34 reports of convulsions with this drug although it would be erroneous to conclude that the incidence of this latter reaction is more than twice that of nephrotoxicity.

2) The absolute number of reported reactions to a particular drug or product clearly is inevitably some function of its usage. Ideally, usage should be expressed as the number of exposed patients but such denominators are impossible to obtain for the UK as a whole. An indication of usage may be obtained from general practitioner prescribing statistics collected (for the NHS) by the Prescription Pricing Authority (PPA), or by the independent organisation Intercontinental Medical Statistics (IMS). Such prescribing data excludes hospitals, although crude estimates can be made from sales or purchasing figures. The PPA's prescription analyses cannot distinguish between 'first-time' and 'repeat' prescriptions, and are incapable of providing usage data by age, gender, or clinical indication. IMS can, however, provide analyses of prescription data by age, gender, clinical indication and dose, although sample sizes in subgroups may be small.

With appropriate prescription data it is possible to calculate adverse reaction reporting 'rates' expressed per million prescriptions. Indeed, by analysing both reports and prescriptions by age and gender, it is possible to examine and compare reporting rates in subgroups of the population (Bateman *et al.*, 1985, 1986). Although such estimates can be used for a variety of purposes (see Part 2), it is important to realise that they are meaningless for products primarily used in hospitals, and that they can provide (at best) only a minimum estimate of incidence.

3) Adverse reaction reporting rates (per million prescriptions) of a particular drug in relation to its prescribing are often a function of its marketing life, with the highest reporting (of both severe and minor reactions) occurring during the first 2 years. This trend is inevitable. First, the CSM only asks doctors to report *all* adverse reactions for the first three or four years after licensing: thereafter, the Committee requests for reporting to be limited to *serious* reactions. Second, with increasing experience of a product's potential hazards, doctors' prescribing may change in order to minimise toxicity: examples include initiating treatment with a lower dosage (e.g. prazosin, captopril, enalapril), avoiding early re-exposure (e.g. halothane), or limiting usage in vulnerable patient populations. Third, there is a tendency for doctors to cease reporting those reactions which are widely recognised. Finally, as a product becomes established in clinical practice, an increasing proportion of users will represent a selected group of patients who tolerate it without adverse sequelae. Comparisons of adverse reaction reporting rates between different products are therefore of doubtful validity unless they are based on comparable sales periods. Weber (1986) has suggested that the logarithm of the cummulative number of reported reactions is a linear function of the logarithm of the cummulative number of prescriptions. Such an approach, however, has serious statistical limitations (Sutherland, 1986).

4) The year of a drug's introduction may also affect the conclusions that can be drawn from comparative reporting rates. As discussed previously, the annual number of spontaneous adverse reaction reports has increased by nearly three-fold, in the UK, since the early 1970s. Whether or not this phenomenon applies to all classes of compounds, and all types of reactions,

is difficult to assess but the possibility must be taken into account. In the USA, where annual reporting rates have risen much more sharply in the last few years, Rossi *et al.* (1987) have corrected their analyses of adverse reporting rates to NSAIDs to take account of these secular changes.

5) Not surprisingly, adverse reaction reporting tends to increase when doctors' attention is drawn to specific problems. For example, between 1964 and 1985 the CSM had received only 17 reports of the neuroleptic malignant syndrome, yet publication of a brief article (Committee on the Safety of Medicines, 1986b) prompted reporting of a further 34 suspected cases.

6) Comparisons of reporting rates to drugs within the same therapeutic class, even when corrected for prescription volume, marketing life, and possibly changes in secular reporting trends, assume that comparable cohorts of patients receive the particular drugs under consideration. That this is not necessarily the case is obvious, and the reporting of reversible airways obstruction with β-adrenoceptor blockers typifies the difficulties. Thus number of reports of asthma, worsening of asthma, or bronchospasm is substantially greater with atenolol (56) than with propranolol (21). It would be erroneous to conclude, from these data, that atenolol is *more* likely to cause bronchospasm than propranolol. The real explanation is likely to be that where doctors feel they need to treat asthmatics or chronic bronchitics with a β-adrenoceptor blocker they will use a relatively selective agent such as atenolol which virtually ensures its over-representation as a cause of reversible airways obstruction.

Conclusions

As with all other spontaneous reporting schemes the CMS's adverse drug reaction register is a biased, incomplete, and unrepresentative database. Yet it represents the only epidemiological surveillance system which routinely monitors the safety of all drugs from the first day of marketing, irrespective of the method of supply or sale, throughout their life as therapeutic agents. The value of a scheme which might appear, at first sight, to be so unpromising is discussed in Part 2 (Rawlins, 1988).

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(Received 11 January 1988, accepted 23 March 1988)